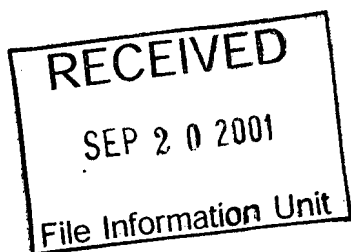


PTO/SB/68 (11-95)

Approved for use through 10/31/99. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)



In re Application of

Application Number

Filed

Group Art Unit

Examiner

07-566977

8-13-90

Paper No. #19

Assistant Commissioner for Patents
Washington, DC 20231

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE:

- ___ (A) referred to in United States Patent Number 5623065 column _____
- ___ (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____, filed _____, on page _____ of paper number _____
- ___ (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____, filed _____, or
- ___ (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

Signature

ADIZIAN

RECEIVED

Date

SEP 20 2001

FOR PTO USE ONLY

File Information Unit



US005623065A

United States Patent [19]

[11] Patent Number: 5,623,065

Cook et al.

[45] Date of Patent: Apr. 22, 1997

[54] GAPPED 2' MODIFIED OLIGONUCLEOTIDES

[75] Inventors: Phillip D. Cook, Vista; Brett P. Monia, Carlsbad, both of Calif.

[73] Assignee: Isis Pharmaceuticals, Inc., Carlsbad, Calif.

[21] Appl. No.: 244,993

[22] PCT Filed: Dec. 23, 1992

[86] PCT No.: PCT/US92/11339

§ 371 Date: Jun. 21, 1994

§ 102(e) Date: Jun. 21, 1994

[87] PCT Pub. No.: WO93/11339

PCT Pub. Date: Jul. 8, 1993

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 814,961, Dec. 24, 1991, abandoned, and Ser. No. 566,977, Aug. 13, 1990, abandoned.

[51] Int. Cl.⁶ C07H 21/00; C07H 21/02; C07H 21/04

[52] U.S. Cl. 536/23.1; 536/23.2; 536/23.5; 536/23.51; 536/23.52; 536/23.53; 536/25.1; 536/25.2; 435/91.1; 435/91.2; 435/91.5; 935/6; 935/9; 935/10

[58] Field of Search 514/44; 536/23.1, 536/23.2, 23.5, 23.51, 23.52, 23.53, 25.1, 25.2; 435/91.1, 91.2, 91.4, 91.5; 935/9, 6, 10

[56] References Cited

U.S. PATENT DOCUMENTS

4,867,187 9/1989 Duck 435/6
 4,908,307 3/1990 Rodland et al. 435/6
 5,013,830 5/1991 Ohtsuka et al. 536/25.1
 5,034,506 7/1991 Summerton et al. 528/391
 5,134,066 7/1992 Rogers et al. 435/91.3
 5,149,797 9/1992 Pederson et al. 536/23.1
 5,220,007 6/1993 Pederson et al. 536/23.1
 5,256,775 10/1993 Froehler 536/25.6
 5,366,878 11/1994 Pederson et al. 435/91.3
 5,403,711 4/1995 Walder et al. 435/6
 5,466,786 11/1995 Buhr et al. 536/26.26

FOREIGN PATENT DOCUMENTS

2017369 11/1990 Canada .
 260032 8/1987 European Pat. Off. .
 365627B1 3/1989 European Pat. Off. .
 0339842 4/1989 European Pat. Off. .
 0339330 11/1990 European Pat. Off. .
 3915462 9/1990 Germany .
 4110085 10/1992 Germany .
 3-240795 of 1991 Japan .
 89/05358 6/1989 WIPO .
 WO90/15814 6/1990 WIPO .
 WO91/06556 10/1990 WIPO .
 WO91/15400 4/1991 WIPO .

OTHER PUBLICATIONS

Block et al. 1988 *Gene* 72, 349-360.
 Cormier et al. 1988 *Nuc. Acids Res.* 16(10), 4583-4594.
 Uhlmann et al. 1990 *Chemical Reviews* 90(4), 544-584.
 Ikchra et al. 1977 *Nuc. Acids Res.* 4(12): 4249-4260.
 Berkowitz et al. 1973 *J. Medicinal Chemistry*, 16(2): 813-814.
 Kawasaki et al. 1991 (Jan.) "Synthesis and Biophysical Studies of 2'-dRIBO-F Modified Oligonucleotides", Conference on Nucleic Acid Therapeutics, Clearwater, FL.
 Agrawal, S. et al., "Oligodeoxynucleoside Phosphoramidates and Phosphorothioates as Inhibitors of Human Immunodeficiency Virus" *Proc. Natl. Acad. Sci. USA* 1988 85, 7079-7083.
 Augustyns, et. al., "Influence of the Incorporation of (S)-9-(3,4-dihydroxy-butyl)Adenine on the Enzymatic Stability and Base-Pairing Properties of Oligodeoxynucleotides" *Nucleic Acids Research* 1991, 19, 2587-2593.
 Beaton, et. al., Chapter 5, Synthesis of oligonucleotide phosphorodithioates, p. 109, *Oligonucleotides and Analogs, A Practical Approach*, Eckstein, F., Ed.; The Practical Approach Series, IRL Press, New York, 1991, pp. 109-135.
 Borthwick, et al., "Synthesis of Chiral Carbocyclic Nucleosides" *Tetrahedron* 1992, 48, 571-623.
 Brill et al., "Synthesis of Deoxydinucleoside Phosphorodithioates", *J. Am. Chem. Soc.* 1991 113, 3972-3980.
 Cohen in *Oligonucleotides: Antisense Inhibitors of Gene Expression*, CRC Press, Inc., Boca Raton, FL (1989), pp. 1-255.
 Dagle et al., "Physical properties of oligonucleotides containing phosphoramidate-modified internucleoside linkages", *Nucleic Acids Research* 1991 19, 1805-1810.
 Dagle et al., "Targeted degradation of mRNA in *Xenopus* oocytes and embryos directed by modified oligonucleotides: studies of An2 and cyclin in embryogenesis", *Nucleic Acids Research* 1990 18, 4751-4757.
 Dagle et al., "Pathways of Degradation and Mechanism of Action of Antisense Oligonucleotides in *Xenopus laevis* Embryos", *Antisense Research and Development* 1991 1, 11-20.
 Debart et al., "Intermolecular Radical C-C Bond Formation: Synthesis of a Novel Dinucleoside Linker for Non-anionic Antisense Oligonucleosides", *Tetra. Ltrs.* 1992 33, 2645-2648.

(List continued on next page.)

Primary Examiner—Christopher S. F. Low
 Attorney, Agent, or Firm—Woodcock Washburn Kurtz Mackiewicz & Norris

[57] ABSTRACT

Oligonucleotides and other macromolecules are provided that have increased nuclease resistance, substituent groups for increasing binding affinity to complementary strand, and subsequences of 2'-deoxy-erythro-pentofuranosyl nucleotides that activate RNase H enzyme. Such oligonucleotides and macromolecules are useful for diagnostics and other research purposes, for modulating protein in organisms, and for the diagnosis, detection and treatment of other conditions susceptible to antisense therapeutics.